

Remarks

Claims 1, 15, 23, 26 and 46 are amended.

Claims 15 and 26 are amended to correct the misspellings objected to.

The prosecution histories of United States Patent Application Serial Numbers 10/121,076 and 10/826,843 contain Office Actions that Examiner may find relevant to the present case.

Claim Rejections – 35 USC § 102

Claims 1, 13, 33-35, 46-50 and 54 were rejected as allegedly being anticipated by Lipari (US 4,383,992). “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” MPEP 2131. Lipari does not teach a cyclodextrin derivative, i.e. a cyclodextrin that has been chemically modified (see p. 2 line 18 to p. 3, line 5 of the specification). Therefore, “each and every element” of the claim is not found in Lipari. Thus, Lipari does not anticipate the claims, and the rejection is improper.

Claim Rejections – 35 USC § 103

Claims 2-12, 14-32, 36-37, and 51 were rejected as allegedly being obvious over Lipari in view of Loftsson (4,383,992). Applicants decline to discuss the details of the dependent claims, but will show that the broad independent claims are not obvious, and thus the dependent claims are not obvious as well. “When applying 35 U.S.C. 103...[t]he references must be considered as a whole and *must suggest the desirability* and thus the obviousness of making the combination.” MPEP 2141 (II)(B) citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). “The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art.” *Custom Accessories, Inc. v. Jeffrey-Allan Indust., Inc.*, 807 F.2d 955, 962, 1 U.S.P.Q.2D (BNA) 1196 (Fed. Cir. 1986). Thus, prior art that suggests that the claimed combination is not desirable suggests that the claims are not obvious.

Examiner cited a patent by Loftsson. A person of ordinary skill in the art considering the teachings of Loftsson’s ‘992 patent will surely consult other writings authored by Loftsson in determining what direction to take work based upon the patent. For example, the paper entitled “Cyclodextrins in ophthalmic drug delivery” by Loftsson (*Advanced Drug Delivery Reviews* 36 (1999) 59–79; hereinafter “Loftsson Paper”) would surely be considered. This reference teaches away from the combination of prednisolone acetate and a cyclodextrin derivative by teaching that carboxylic acid prodrugs are unstable in the presence of cyclodextrins and cyclodextrin derivatives, and that cyclodextrins and cyclodextrin derivatives may decrease the bioavailability of steroids in ophthalmic formulations.

The prior art teaches that prednisolone acetate would be unstable in the presence of a cyclodextrin derivative.

The Loftsson Paper specifically teaches that “drug *degradation may be increased* upon complexation if the hydrolytically labile ester linkage of the drug is in a close vicinity of the hydroxyl group of CD molecule. The reaction has been explained to proceed via nucleophilic attack by the hydroxyl group of the CD on the carbonyl carbon of the *ester linkage*, resulting in a covalent intermediate and subsequent hydrolysis of product.” (p. 68, left column, 9 lines down). In other words, a cyclodextrin or cyclodextrin derivative can catalyze ester hydrolysis. Hydrolysis is particularly problematic for ophthalmic compositions because the active agents are stored in an aqueous liquid. A person of ordinary skill in the art knows that prednisolone acetate is an ester prodrug, and will thus avoid using it with a cyclodextrin derivative to avoid hydrolysis.

Prednisolone acetate topical ophthalmic preparations are currently marketed in suspension form. The suspension form has a stabilizing effect on the prednisolone acetate. A suspension only has contact with the aqueous environment at the interface between a suspended particle and the aqueous solution. A significant portion of the drug is in suspended particles, but is not part of the interface. This non-interfacial drug is protected from the aqueous environment, and is not susceptible to hydrolysis. But enhancing the solubility of a drug brings more of it into contact with the aqueous environment, making it more susceptible to hydrolysis. Adding a cyclodextrin derivative to prednisolone acetate is expected to enhance its solubility, and would thus make prednisolone acetate more susceptible to hydrolysis and less stable.

Therefore, the Loftsson Paper teaches away from the claimed combination due to an expectation of substantially reduced stability of prednisolone acetate compared to the commercial formulation. This substantially reduced stability arises from two changed circumstances: 1) the catalysis of hydrolysis by cyclodextrin derivatives, and 2) the increased availability of the compound for hydrolysis due to the increased solubility of the drug.

The prior art teaches that cyclodextrin can reduce the bioavailability of topical ophthalmic steroid compositions.

The Loftson Paper suggests that prednisolone bioavailability will be reduced if cyclodextrin is added to a prednisolone acetate ophthalmic. It states that “coadministration of HP- β -CD (90 mM) decreased the ophthalmic bioavailability of hydrocortisone (1% solution) compared to its 1% suspension.” (p. 72, left column, middle of page). Hydrocortisone is a corticosteroid. If coadministration of hydroxypropyl- β -cyclodextrin decreased the bioavailability of one corticosteroid as compared to its 1% suspension, one of ordinary skill will reasonably expect that the use of a cyclodextrin derivative would reduce bioavailability of another corticosteroid as compared to its 1% suspension. This suggests that attempting to formulate prednisolone acetate with a cyclodextrin derivative will reduce bioavailability as compared to the

commercially available 1% suspension. Thus, the Loftsson Paper suggests that the claimed combination would be less bioavailable than the commercial product.

Hydrocortisone is not an exception. The Loftsson Paper warns that use of cyclodextrins in formulating hydrophobic drugs in general for ophthalmic administration is not straightforward: “there are some basic differences between ophthalmic administration of cyclodextrins and administration of cyclodextrin via other routes. These differences have induced some limitations in the ophthalmic application of these most recently developed pharmaceutical excipients.” (Abstract, lines 3-7) The Loftsson Paper further observes that “[s]everal in vitro and in vivo studies have shown that excess complexation of a poorly water-soluble drug will decrease its membrane permeability and ophthalmic bioavailability.” (p. 72, left column, first sentence, first full paragraph.)

Furthermore, Watson *et. al.* have shown that the commercial 1% prednisolone acetate ophthalmic suspension gave the highest concentration of steroid of any of the commercially available topical ophthalmic steroids at the time of their study. (See Loftsson and Stefansson, *Acta Ophthal. Scand.* 2002: 80: 144-150, enclosed, p. 145, top of middle column).

Thus, when a person of ordinary skill in the art considers

- 1) that a cyclodextrin derivative actually reduced the bioavailability of a aqueous hydrocortisone solution as compared to an aqueous hydrocortisone suspension,
 - 2) the difficulty in formulating poorly water-soluble drugs in general for ophthalmic administration, and
 - 3) the already high bioavailability of the prednisolone acetate suspension,
- she would be discouraged from making or using the claimed compositions. Thus, the prior art suggests that the claimed composition is not desirable, and the claims are not obvious. Thus, the prior art teaches away from the claimed composition.

Alternatively, no *prima facie* case of obviousness was made because there is no reasonable expectation of success.

Therefore, the claims are not *prima facie* obvious.

Unexpected Results

Even if a *prima facie* case of obviousness were made, it would be overcome with the unexpected results presented in the specification. Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. MPEP 2144.08 (b)(6) Unexpected results are shown in relation to the closest prior art, but the closest prior art need not be something relied upon by Examiner. *In re Holladay*, 584 F.2d, 384, 386 (CCPA, 1978). Thus, there are two relevant questions: 1) what is the closest prior art, and 2) does the claimed invention have unexpected results with regard to that art? Applicant will show that the claimed invention does have unexpected results with regard to the closest prior art.

The Closest Prior Art

Although Examiner cited Lipari and Loftsson, they are not the closest prior art. Lipari teaches a combination of prednisolone acetate and unmodified β -cyclodextrin. This combination was not tested because, based upon the information available to Applicants, Applicants did not reasonably expect that it would be useful. β -Cyclodextrin is unsafe for human use and is not soluble enough to provide a solution of prednisolone acetate. For example, Mosher and Thompson (Encyclopedia of Pharmaceutical Technology, Marcel-Decker 2002, pp. 531-558, 548) disclose that “the parent [unmodified] CDs can all show a toxic effect on the kidney when given parenterally.” Higuchi teaches that “[unmodified] β -CD exhibits renal toxicity upon systemic administration. The proposed mechanism of β -CD or a β -CD: cholesterol complex inside the renal tubule cell.” (“Cyptisol: SBE7- β -cyclodextrin: A new drug formulation system;” CyDex Inc., Overland Park, Kansas, p. 4.) Furthermore, it is doubtful that Lipari’s composition would in fact form an aqueous solution. Thompson teaches that [unmodified] “ β -CD is the least soluble cyclodextrin.” (Critical Reviews in Therapeutic Drug Carrier Systems, 14(1): 1-104 (1997.)) Thus, Lipari’s composition is not suitable for human use because of its toxicity, and is not likely to form a stable composition at the prednisolone acetate concentrations desired. Therefore, Lipari is not the closest prior art.

Loftsson does not teach the use of prednisolone acetate, which is the most important feature of the composition, since it is the active component. By contrast, the commercial prednisolone acetate suspension provides the same active component, and only differs in that it does not have the excipient cyclodextrin derivative. Thus, the commercial prednisolone acetate suspension is the closest prior art.

*The unexpected results***The prior art suggests that cyclodextrin will not facilitate delivery of prednisolone from the aqueous humor to the vitreous humor.**

The Loftsson Paper suggests that cyclodextrin should not affect delivery of prednisolone from the aqueous humor to the vitreous humor. In discussing ophthalmic compositions of steroids, it states “[f]or diseases of the posterior segments of the eye, systemic administration is required.” (p. 74, right column, section 9.2, end of first paragraph.) Loftsson believes that any bioavailability enhancement attributed to cyclodextrin is due to the ability of cyclodextrin to get more drug into solution, and not to any enhanced membrane permeability attributed to cyclodextrin or complexes between cyclodextrins and drugs. Consider the following statements in the Loftsson Paper: “[i]n general, the natural CDs and their hydrophilic derivatives are only able to penetrate lipophilic biological membranes, such as the eye cornea, *with considerable difficulty*.” (p. 62, under “3. Toxicological considerations,” second sentence.) “It is not likely that large hydrophilic CD molecules permeate into those lipophilic membranes.” (p. 63, left column, about $\frac{3}{4}$ from top.) “CD molecules will only permeate biological membranes

with considerable difficulty.” (p. 64, left column, third line from bottom.) The Loftsson Paper further observed “co-administration of HP- β -CD (90 mM) decreased the ophthalmic bioavailability of hydrocortisone (1% solution) compared to its 1% suspension.” (p. 72, left column, middle of page.)

Since the aqueous humor is inside the eye, and “CD molecules will only penetrate biological membranes with considerable difficulty,” one would not expect a cyclodextrin derivative to be found in any appreciable quantity in the aqueous humor of the eye. If no cyclodextrin derivative is not found in the aqueous humor of the eye, then one would not expect a cyclodextrin derivative to assist passage of a drug from the aqueous humor to the vitreous humor. Thus, if two prednisolone compositions deliver similar amounts of prednisolone or prednisolone acetate to the aqueous humor, one of ordinary skill in the art would not expect the presence of a cyclodextrin derivative in the topical composition to have a noticeable effect upon the prednisolone concentration in the vitreous humor.

Unexpectedly, cyclodextrin appears to facilitate delivery of prednisolone from the aqueous humor to the vitreous humor.

The results presented in the specification suggest that a cyclodextrin derivative does facilitate delivery of prednisolone from the aqueous humor to the vitreous humor. Figure 2 shows the prednisolone or prednisolone acetate concentration in the aqueous humor for three compositions that contain a cyclodextrin derivative (2b, 2c, and 2f). The prednisolone or prednisolone acetate concentration in the aqueous humor for these three compositions are the same, within experimental error, to that of the commercial composition (2g). However, Figure 3 shows that the three compositions containing a cyclodextrin derivative (2b, 2c, and 2f) do deliver an observable amount of prednisolone to the vitreous humor while, the commercial composition (2g) does not. Figure 4 shows the aqueous humor and vitreous humor concentrations side by side, and the large observable difference between the claimed compositions and the commercial composition is undeniable.

These results demonstrate that the present compositions provide delivery from the aqueous humor to the vitreous humor. By contrast, the commercial prednisolone suspension, which provides the same concentration of prednisolone in the aqueous humor, does not. As established above, the prior art leads one to the conclusion that there should be no difference between the compositions containing a cyclodextrin derivative and commercial formulations. Therefore, the results are unexpected, and the claimed compositions are not obvious over the prior art.

Double Patenting

Applicants submit herewith a terminal disclaimer for United States Patent Numbers 6,969,706; 6,723,353; and 6,358,935. Therefore, Applicants respectfully request that this rejection be removed.

In light of the amendments, arguments, and terminal disclaimers made herein, Applicants respectfully request that Examiner remove the rejections and pass the application to issue.

Please charge Deposit Account 01-0885 for any fees related to this response.

Respectfully submitted,

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